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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/180,269	07/08/1999	KATHRYN LINDSAY BALL	CCI-007US	6599

7590 10/22/2002

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EXAMINER
MURPHY, JOSEPH F

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/22/2002 21

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/180,269	BALL ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Peri d f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *2,6,8,10-12,17,44-47 and 51-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 6, 8, 10-12, 17, 44-47, 51-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/29/2002 has been entered.

Formal Matters

Claims 31-43 and 48-50 were cancelled, and new claims 51-56 were added in Paper No. 20, 7/29/2002. Claims 2-12, 17, 44-47, 51-56 are pending. Claims 3-5, 7, 9 stand withdrawn from consideration pursuant to 37 CFR 1.142(b). Claims , 6, 8, 10-12, 17, 44-47, 51-56 are under consideration.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 6, 8, 10-12, 17, 44-47, 51-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a compound which decreases binding between p21 and cyclin D1, does not reasonably provide enablement for a method for identifying a compound which decreases binding between a derivative or analogue or fragment of p21 and a derivative or analogue of cyclin D1 does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 2, 6, 8, 10-12, 17, 44-47, 51-56 are overly broad in the recitation of "derivative" and "analogue" and "fragment "since insufficient guidance is provided as to which of the myriad of polypeptide species encompassed by the claim will retain the characteristics of p21 or cyclin D1. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible muteins of p21 or cyclin D1. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph).

Since the claims encompass p21 or cyclin D1 fragments, derivatives or analogues, and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to practice the claimed method. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors considered to be relevant in the instant case are set forth below:

(1) the breadth of the claims - The claims are drawn to a method for identifying a compound which decreases binding between a fragment, derivative or analogue of p21 and a derivative or analogue of cyclin D1.

(2) the nature of the invention - The instant invention is a method of compound identification.

(3) the state of the prior art - The Voet reference demonstrates that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function.

(5) the level of predictability in the art - The Voet reference demonstrates the unpredictability of the protein art.

(6) the amount of direction provided by the inventor - Applicant has only taught methods using p21 or cyclin D1, not fragments, derivatives or analogues of p21 or cyclin D1.

(7) the existence of working examples - Working examples are provided only for p21 or cyclin D1, not fragments, derivatives or analogues of p21 or cyclin D1.

(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Given the breadth of claims 2, 6, 8, 10-12, 17, 44-47, 51-56 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to practice the claimed invention.

Claims 2, 6, 8, 10-12, 17, 44-47, 51-56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

These are genus claims. Because of the use of the terms fragments, derivatives or analogues in the claims, the claims encompass proteins having one or more amino acid substitutions, deletions, insertions and/or additions made to cyclin D1 or p21. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to cyclin D1 or p21. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Although the specification states that these types of changes are routinely done in the art, the specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because

specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, cyclin D1 or p21 alone are insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed derivatives or analogues of cyclin D1 or p21 to be used in the method of identifying a compound.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-11, 17, 46, 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10, 17, 46 and 47 are vague and indefinite in the recitation of the term "modulates". It is not clear whether the claims are drawn to methods which identify agonists or antagonists of the cyclin D1 p21 interaction. Claim 11 is rejected insofar as it depends on the recitation of "modulates" in claim 10.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 6, 8, 10-12 and 17 stand rejected, and claims 44-47, 51-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/09135 (Beach et al.) in view of Xiong et al. (1993), for reasons of record set forth in Paper No. 16, 10/23/2001.

Beach et al. discloses the association between cyclin D, p21 and cdk 4, and its disruption upon introduction of SV40 tumor virus or its gene product (page 3, lines 35-36). Beach et al. discloses that inhibitors of p21 can be introduced into cells and interfere with p21 binding to complex members (i.e. including cyclin D) (page 4, line 27-28). Beach et al. also discloses that drugs which alter p21 function can be used to inhibit or enhance cell division (page 25, lines 22-23). Beach discloses a method of screening compounds for their ability to inhibit or suppress the transformation of a cell, which may include prevention of formation of complexes including

cyclin D, p21 and CDK (page 24, line 12 to page 25, line 9). Beach et al. teaches that it is possible to selectively decrease mitotic capability of cells by the use of an agent, which is designed to interfere with the activity of a complex comprising a particular D type cyclin and CDK. Beach et al. teaches screening of a compound which selectively inhibits interaction of a D-type cyclin with CDK4 (page 25, lines 16-20). Beach discloses that drugs which alter p21 function can be used to inhibit or enhance cell division (page 25, lines 22-23), and that these drugs can be small peptides which mimic the complex constituent in terms of binding but which lacks its active regions (page 25, lines 25-26).

Beach et al. does not list the sequence of p21, hence the Xiong et al. reference is cited to exemplify that the sequence of p21 comprises the claimed KRRLIFSK sequence (see Sequence Comparison A, attached). Therefore, it would have been obvious to one of skill in the art at the time the invention was made to practice the method disclosed in Beach et al. to screen for a compound which modulates the interaction of p21 and cyclin D and cdk 4. The motivation is provided in Beach et al. which discloses that p21 is known to associate with cyclin kinases only in normal, untransformed cells, and thus offers specificity in modulating cell division, for example the ability to selectively alter cell division in particular cell types or at a particular point in the cell cycle (page 4, lines 7-15). The expectation of success is provided by Beach et al., which teaches that agents which selectively inhibit cyclin D1 are expected to be particularly useful (page 25, lines 1-6).

Applicant argues that the teaching of Beach et al. is an invitation to experiment. However, see In re O 'Farrell, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (citations omitted) where the court held the claimed method would have been obvious over the

prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful. MPEP § 2145. Here, the Beach et al. reference contains an enabling disclosure, a suggestion to modify the prior art to produce the claimed invention (page 25, lines 22-26), and a suggestion that the modification would be successful (page 25, lines 1-6).

Applicant further argues that the references fail to teach peptide fragments of p21, however, Beach discloses that drugs which alter p21 function can be used to inhibit or enhance cell division (page 25, lines 22-23), and that these drugs can be small peptides which mimic the complex constituent in terms of binding but which lacks its active regions (page 25, lines 25-26). Therefore, the Beach reference teaches that peptides derived from p21 can be used to inhibit cyclin D1 complex formation, and Beach also discloses methods of identifying such peptides.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
October 16, 2002